MC
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re. Patent of:	Norbert Busch et al.
Patent Number:	Re. 30,577
Issued:	April 14, 1981, reissue of U.S. Patent No. 3,962,238 issued June 8, 1976
For:	ETHER OF N-PROPANOL AMINE

Box Pat. Ext.
Commissioner of Patents and Trademarks
Washington, DC 20231

LETTER OF TRANSMITTAL OF APPLICATION
FOR EXTENSION OF PATENT TERM

Sir:

Enclosed herewith are the application papers seeking an extension of the patent term of U.S. Patent No. Re. 30,577 pursuant to the provisions of 35 U.S.C. 156 and 37 C.F.R. 1.740.

The application papers consist of:

1. Power of Attorney
2. Declaration by patent owner
3. Application for Extension with attachments.

A duplicate of the application papers, certified as such, are also included.

Please charge the filing fee of $600.00 required pursuant to 37 C.F.R. Section 1.20(n) to Deposit Account 03-0935.

The Commissioner is authorized to charge any additional filing or other fees or credit any overpayment to Deposit Account 03-0935. Two additional copies of this letter are enclosed.

Respectfully submitted,

Riom Laboratories C.E.R.M.
Applicant

By: Kevin B Clarke
Kevin B. Clarke, Esq.
Attorney for Applicant
Registration No. 22,647
Carter-Wallace, Inc.
1345 Avenue of the Americas
New York, New York 10105

CERTIFICATION UNDER 37 CFR 1.10

I hereby certify that this Application for Extension of Patent Term Transmittal and the documents referred to as enclosed therein are being deposited with the United States Postal Service on this date February 22, 1991 in an envelope as "Express Mail Post Office to Addressee" Mailing Label Number 409773782 addressed to Box Pat. Ext., Commissioner of Patents and Trademarks, Washington, D.C. 20231.

Kevin B. Clarke, Esq
Type name of person mailing paper

Kevin B Clarke

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409773782

#19

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent of: Norbert Busch et al.

Patent Number: Re. 30,577

Issued: April 14, 1981, reissue of U.S. Patent No. 3,962,238 issued June 8, 1976

For: ETHER OF N-P[illegible]ANOL AMINE

Commissioner of Patents and Trademarks
Washington, DC 20231

POWER OF ATTORNEY

Dear Sir:

Riom Laboratories C.E.R.M. (formerly known as Centre Europeen de Recherches Mauvernay "CERM") located at Riom, France represents that it is the assignee of the entire interest in and to Letters Patent of the United States No. Re. 30,577, granted to Norbert Busch et al. by virtue of an assignment of such patent recorded February 27, 1973, Reel 2943, Frames 178-179 and hereby appoints

Kevin B. Clarke, Esq.
Reg. No. 22,647
Carter-Wallace, Inc.
1345 Avenue of the Americas
New York, NY, U.S.A. 10105

its attorney, to apply for an extension of the term of said patent, to make alterations and amendments therein, and transact all business in the United States Patent Office connected therewith, and request that all further correspondence be conducted with Kevin B. Clarke at the above address.

Respectfully submitted,

Riom Laboratories C.E.R.M.

By: Jean M. Barnerias

Title: President

Date: 8.02 1991

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re. Patent of: Norbert Busch et al.

Patent Number: Re. 30,577

Issued: April 14, 1981, reissue of U.S. Patent No. 3,962,238 issued June 8, 1976

For: ETHER OF N-PROPANOL AMINE

Box Pat. Ext.
Commissioner of Patents and Trademarks
Washington, DC 20231

DECLARATION IN SUPPORT OF APPLICATION
FOR PATENT EXTENSION UNDER 37 C.F.R. 1.740(b)

Dear Sir:

I, Jean Michel Barnerias, agent of owner of record, Riom Laboratories C.E.R.M. (formerly known as Centre European de Recherches Mauvernay "CERM") of U.S. Patent No. Re. 30,577, residing at Riom, France hereby declare as follows:

(1) This declaration is submitted in support of owner's Application for Extension of Patent Term for U.S. Patent No. Re. 30,577, filed simultaneously herewith.

(2) I am an official of the owner of record of U.S. Patent No. Re. 30,577 and am authorized to act on behalf of said owner.

(3) Wallace Laboratories, Division of Carter-Wallace, Inc., the holder of approved NDA No. 19-001 covering the product Bepadin, is a Licensee of owner under U.S. Patent No. Re. 30,577.

(4) I have reviewed and understand the contents of the owner's Application for Extension of Patent Term for U.S. Patent No. Re. 30,577 being submitted herewith pursuant to 37 C.F.R. 1.740.

(5) I believe that U.S. Patent No. Re. 30,577 is subject to extension pursuant to 37 C.F.R. 1.740 and believe that an extension of the length claimed in the Application for Extension of Patent Term for U.S. Patent No. Re. 30,577 filed simultaneously herewith is justified under 35 U.S.C. 156 and the applicable requirements.

(6) I believe that U.S. Patent No. Re. 30,577 for which extension is being sought meets the conditions for extension of the term of a patent as set forth in 37 C.F.R. 1.720.

I further state that the above statements were made with the knowledge that willful false statements and the like are punishable by fine or imprisonment or both under Section 1001 of Title 18 of the United States Code and that any willful false statements may jeopardize the validity of U.S. Patent No. Re. 30,577.

Riom Laboratories C.E.R.M.

By: Jean M. Barnerias

Title: president

Date: 8.02.1991

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re. Patent of: Norbert Busch et al.

Patent Number: Re. 30,577

Issued: April 14, 1981, reissue of U.S. Patent No. 3,962,238 issued June 8, 1976

Expires: June 8, 1993

For: **ETHER OF N-PROPANOL AMINE**

Box Pat. Ext.
Commissioner of Patents and Trademarks
Washington, DC 20231

APPLICATION FOR EXTENSION OF PATENT TERM
UNDER 35 U.S.C. 156

Dear Sir:

Applicant, Riom Laboratories C.E.R.M. (formerly known as Centre European de Recherches Mauvernay), represents that by virtue of an assignment recorded on February 27, 1973, at Reel 2943, Frame 178-179, it is the assignee of the entire interest in and to Letters Patent of the United States No. Re. 30,577, granted to Norbert Busch et al. The claims of U.S. Patent No. Re. 30,577 cover the approved product bepridil hydrochloride.

Pursuant to a license agreement dated September 1, 1975, Applicant granted Carter-Wallace, Inc. through its Wallace Laboratories Division the exclusive right, with the right to grant sublicenses, to make, have made, use and sell the product bepridil hydrochloride in the United States of America together with the right to apply for, obtain and/or maintain investigational new drug exemptions ("IND's"), new drug applications ("NDA's") or other government clearances or approvals to market bepridil hydrochloride.

As a result of a sublicense agreement dated January 4, 1982, Carter-Wallace, Inc. granted McNeilab, Inc. and its parent, Johnson & Johnson, a sublicense under the rights granted to Carter-Wallace, Inc. by Applicant, including the right inter alia to apply for, obtain and maintain IND's and

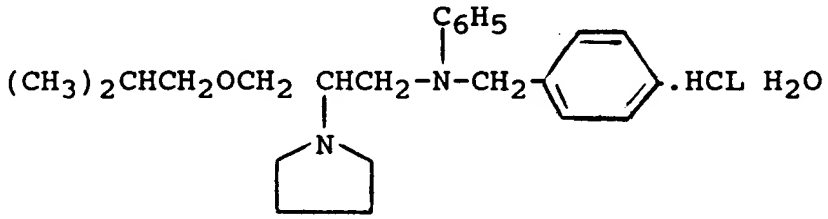
NDA's or other government clearances or approvals to market bepridil hydrochloride.

Pursuant to the sublicense agreement dated January 4, 1982, McNeilab agreed to carry out all required testing and development work to enable Wallace Laboratories and McNeilab to obtain and maintain approved NDA's covering bepridil hydrochloride . The parties agreed to provide each other with written authorization so as to enable each party to refer to the others IND, NDA and all other applications and documents relating to approvals or maintaining approvals for use or marketing of bepridil hydrochloride.

Bepridil hydrochloride NDA's No. 19-001 (Wallace Laboratories bepridil hydrochloride known as BEPADIN) and No. 19-002 (McNeilab's bepridil hydrochloride known as VASCOR) were simultaneously approved on December 28, 1990.

Applicant hereby submits this application for extension of patent term under 35 U.S.C. 156, providing the following information as required by 37 C.F.R. 1.740:

(1) The approved product BEPADIN/VASCOR is bepridil hydrochloride and has the following structure:



(2) The approved product, BEPADIN/VASCOR, was subject to regulatory review under the Federal Food, Drug and Cosmetic Act (21 U.S.C. 355), Section 505.

(3) BEPADIN/VASCOR received permission for commercial marketing or use under Section 505 of the Federal Food, Drug and Cosmetic Act (21 U.S.C. 355) on December 28, 1990.

(4) This application for extension of patent term under 35 U.S.C. 156 is being submitted within the sixty (60) day period permitted for submission, the last day for said submission being February 25, 1991.

(5) The complete identification of the patent for which an extension is being sought is as follows:

Inventors: Norbert Busch
Jacques Simond
Andre Monteil
Jacques Moleyre
Roland Y. Mauvernay

Patent No.: Re. 30,577

Reissued: April 14, 1981 - reissue of U.S. Patent No. 3,962,238 issued June 8, 1976

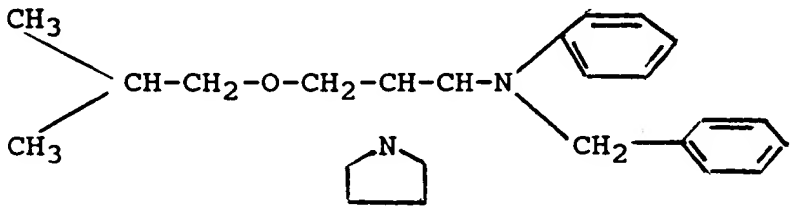
Expiration Date: June 8, 1993

(6) A copy of the patent for which an extension is being sought is attached herewith together with a copy of U.S. Patent No. 3,962,238 as "Attachments A and B", respectively.

(7) No disclaimer, receipt of maintenance fee payment or re-examination certificate has been issued with respect to U.S. Patent No. Re. 30,577.

(8) U.S. Patent No. Re. 30,577 claims the product bepridil hydrochloride, as identified in paragraph (1) hereinabove. More specifically, the product is claimed in claims 7 and 8 of U.S. Patent No. Re. 30,577 as follows:

"7. An ether having the formula:



and pharmaceutically acceptable acid addition salts thereof."

"8. An ether according to claim 7 wherein the acid addition salt is the hydrochloride or the acid fumarate."

(9) The relevant dates and information pursuant to 35 U.S.C. 156 to enable the Secretary of Health and Human Services to determine the length of the applicable regulatory review period are as follows:

(a) U.S. Patent No. Re. 30,577 was reissued on April 14, 1981, as a reissue of U.S. Patent No. 3,962,238 which issued on June 8, 1976. U.S. Patent No. Re. 30,577 is set to expire on June 8, 1993;

(b) IND for bepridil hydrochloride (BEPADIN) was filed by Wallace Laboratories on February 18, 1977, received and accorded IND No. 13,238 on February 22, 1977 and was effective March 24, 1977;

(i) A clinical hold was imposed on IND No. 13,238 on March 7, 1977;

(ii) the clinical hold was recinded on March 30, 1978.

(c) IND for bepridil hydrochloride was filed by McNeilab, Inc. (VASCOR) and received on February 15, 1982, accorded IND No. 19,896 and was effective March 17, 1982.

(d) NDAs for bepridil hydrochloride were submitted cooperatively and simultaneously by Wallace Laboratories and McNeilab, Inc. on December 28, 1983 (NDA No. 19-001 BEPADIN and NDA No. 19-002 VASCOR, respectively);

(e) NDA No. 19-001 for BEPADIN and NDA No. 19-002 for VASCOR were simultaneously approved on December 28, 1990.

(10) A brief description of the activities undertaken by the applicant's licensees during the applicable regulatory review period with respect to bepridil hydrochloride and the significant dates applicable to such activities is attached herewith as "Attachment C".

(11) Applicant is of the opinion that U.S. Patent No. Re. 30,577 is eligible for extension under 35 U.S.C. 156 because it satisfies the requirements for such extension as follows:

(a) 35 U.S.C. 156(a)
U.S. Patent No. Re. 30,577 claims the approved product BEPADIN/VASCOR;

(b) 35 U.S.C. 156(a)(1)
The term of U.S. Patent No. Re. 30,577 has not expired before submission of this application for extension;

(c) 35 U.S.C. 156(a)(2)
The term of U.S. Patent No. Re. 30,577 has never been extended;

(d) 35 U.S.C. 156(a)(3)
The application for extension is submitted by the owner of record of U.S. Patent No. Re. 30,577 in accordance with the requirements of 35 U.S.C. 156(d) and the guidelines of the U.S. Patent and Trademark Office;

(e) 35 U.S.C. 156(a)(4)
The product BEPADIN/VASCOR has been subject to a regulatory review period before its commercial marketing or use;

(f) 35 U.S.C. 156(a)(5)(A)
The permission for the commercial marketing or use of the product, BEPADIN/VASCOR, after the regulatory review period, is the first permitted commercial marketing or use of the product under the provisions of the Federal Food, Drug and Cosmetic Act (21 U.S.C. 355) under which such regulatory review period occurred; and

(g) 35 U.S.C. 156(c)(4)
No other patent has been extended for the same regulatory review period for the product BEPADIN/VASCOR.

(12) The length of extension of the patent term of U.S. Patent No. Re. 30,577 claimed by Applicant is two years, the maximum possible under 35 U.S.C. 156(g)(6)(C), since the patent involved was issued before the date of enactment of 35 U.S.C. 156, an exemption under subsection (i) of Section 505 and an application under subsection (b) of Section 505 of the Federal Food, Drug and Cosmetic Act (21 U.S.C. 355) were submitted with respect to the approved product, BEPADIN/VASCOR, before the date of enactment of 35 U.S.C. 156, and the commercial use or marketing of the

product, BEPADIN/VASCOR, was not approved before the date of enactment of 35 U.S.C. 156. The regulatory review period exceeds two years as shown by the following:

(a) The regulatory review period under 35 U.S.C. 156(g)(1)(B) was from March 30, 1978 until December 28, 1990 which is 4,655 days.

(b) The period of review, "Testing Period", under 35 U.S.C. 156(g)(1)(B)(i) was from March 30, 1978 until December 28, 1983, which is 2,098 days.

(c) The period of review, "Application Period" under 35 U.S.C. 156(g)(1)(ii) was from December 28, 1983, until December 28, 1990, which is 2,557 days.

(d) The total regulatory review period under 35 U.S.C. 156(g)(1)(B) 4,655 days is subject to the limitation of 35 U.S.C. 156(g)(6)(C) and therefore the period of extension determined on the basis of the regulatory review period, as determined under 35 U.S.C. 156(g)(1)(B), may not exceed two (2) years.

(e) Under 35 U.S.C. 156(c)(2), the period for extension includes only one-half of the period determined under 35 U.S.C. 156(g)(1)(B)(i), i.e. 1,049 days. In the absence of the limitation noted above, the permissible period of extension for U.S. Patent No. Re. 30,577 would have been 3,606 days.

(f) In compliance with 35 U.S.C. 156(c)(3), the period remaining in the term of U.S. Patent No. Re. 30,577 after NDA approval of BEPADIN/VASCOR is 894 days which when added to the two-year extension period claimed by applicant is 1,625 days, and therefore is not in excess of fourteen (14) years.

(13) Applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services any information which is material to any determination to be made relative to this application for extension.

(14) The prescribed fee for receiving and acting upon this application for extension is to be charged to Deposit Account 03-0935 as authorized in the accompanying letter which is submitted in duplicate. The requisite Declaration, set forth in 37 C.F.R. 1.740(a)(17) and (b) is also attached hereto.

(15) Inquiries and/or other correspondence relating to this application for patent term extension are to be directed to:

Kevin B. Clarke, Esq.
Carter-Wallace, Inc.
1345 Avenue of the Americas
New York, New York 10105

(16) A certified duplicate copy of the application papers is submitted herewith.

Respectfully submitted,

Riom Laboratories C.E.R.M.
Applicant

By: 
Kevin B. Clarke, Esq.
Attorney for Applicant
Registration No. 22,647
Carter-Wallace, Inc.
1345 Avenue of the Americas
New York, New York 10105
(212) 339-5207

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#19

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re. Patent of:	Norbert Busch et al.
Patent Number:	Re. 30,577
Issued:	April 14, 1981, reissue of U.S. Patent No. 3,962,238 issued June 8, 1976
For:	ETHER OF N-PROPANOL AMINE

Box Pat. Ext.
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Washington, DC 20231

LETTER OF TRANSMITTAL OF APPLICATION
FOR EXTENSION OF PATENT TERM

Sir:

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1. Power of Attorney
2. Declaration by patent owner
3. Application for Extension with attachments.

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Please charge the filing fee of $600.00 required pursuant to 37 C.F.R. Section 1.20(n) to Deposit Account 03-0935.

P 30034 03/01/91 RE. 30,577 03-0935 030 111 600.00CH

The Commissioner is authorized to charge any additional filing or other fees or credit any overpayment to Deposit Account 03-0935. Two additional copies of this letter are enclosed.

Respectfully submitted,

Riom Laboratories C.E.R.M.
Applicant

By: Kevin B Clarke
Kevin B. Clarke, Esq.
Attorney for Applicant
Registration No. 22,647
Carter-Wallace, Inc.
1345 Avenue of the Americas
New York, New York 10105

CERTIFICATION UNDER 37 CFR 1.10

I hereby certify that this Application for Extension of Patent Term Transmittal and the documents referred to as enclosed therein are being deposited with the United States Postal Service on this date February 22, 1991 in an envelope as "Express Mail Post Office to Addressee" Mailing Label Number 409773782 addressed to Box Pat. Ext., Commissioner of Patents and Trademarks, Washington, D.C. 20231.

Kevin B. Clarke, Esq
Type name of person mailing paper

Kevin B Clarke

#19

CERTIFICATE

State of New York)
) ss.
County of New York)

I, ARLENE STRICKLAND, a Notary Public of the State of New York hereby certify that the attached Power of Attorney, Declaration in Support of Application for Patent Extension Under 37 C.F.R. 1.740(b) and Application for Extension of Patent Term Under 35 U.S.C. 156 with attachments are each true and accurate duplicates of the application papers being filed with the U.S. Patent Office concurrently herewith in support of an application for extension of patent term respecting U.S. Patent No. Re. 30,577.

Dated: New York, New York
22nd Day of February, 1991.

Arlene Strickland
Notary Public

ARLENE STRICKLAND
NOTARY PUBLIC, STATE OF NEW YORK
NO. 4656451
QUALIFIED IN SUFFOLK COUNTY
CERTIFICATE FILED NEW YORK COUNTY
TERM EXPIRES MARCH 30, 1992

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"ATTACHMENT A"

United States Patent [19]

Busch et al.

[11] E **Re. 30,577**

[45] **Reissued Apr. 14, 1981**

[54] **ETHER OF N-PROPANOL AMINE**

[75] Inventors: Norbert Busch, Louboyrat; Jacques Simond, Chamalieres; André Montoli, Gerzat; Jacques Maleyre, Mozac; Roland Y. Mauvernay, Riom, all of France

[73] Assignee: Centre Europeen de Recherches Mauvernay, Riom, France

[21] Appl. No.: 15,782

[22] Filed: Feb. 27, 1979

Related U.S. Patent Documents

Reissue of:

[64] Patent No.: 3,962,238
Issued: Jun. 8, 1976
Appl. No.: 336,357
Filed: Feb. 27, 1973

[30] Foreign Application Priority Data

Mar. 6, 1972 [FR] France 72.07867

[51] Int. Cl.³ C07D 207/08

[52] U.S. Cl. ..... 260/326.5 L; 260/326.5 R; 424/248.56; 424/267; 424/274; 424/325; 544/124; 544/165; 544/177; 546/194; 546/232; 564/384

[58] Field of Search ..... 260/326.5 L

[56] References Cited

U.S. PATENT DOCUMENTS

2,600,301	6/1952	Kerwin	260/370.9
2,832,795	4/1958	Hempel et al.	260/370.9
3,666,811	5/1972	Van der Steldt	260/370.9

FOREIGN PATENT DOCUMENTS

7207867 3/1972 France .

Primary Examiner—Donald G. Daus
Assistant Examiner—David B. Springer
Attorney, Agent, or Firm—Ohlon, Fisher, Spivak, McClelland & Maier

[57] ABSTRACT

[Ethers] *An ether* of n-propanolamine, preparation thereof and [their] *its* use in treatment of cardiovascular conditions.

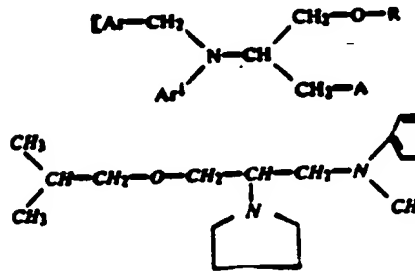
2 Claims, No Drawings

ETHER OF N-PROPANOL AMINE

Matter enclosed in heavy brackets [ ] appears in the original patent but forms no part of this reissue specification; matter printed in italics indicates the additions made by reissue.

This invention relates to [ethers] *an ether* of n-propanolamine, to the preparation thereof and to the use thereof.

The present invention provides an ether of an n-propanolamine having the [general] formula:



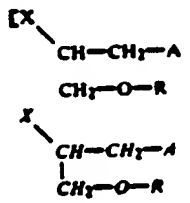
(I)

[in which A is a tertiary aliphatic, cycloaliphatic or heterocyclic amino group, R is a straight or branched chain lower alkyl group or an aralkyl group, Ar is an aromatic group and Ar^1 is an aromatic or heterocyclic group,] and addition salts thereof with pharmacologically acceptable acids.

[When Ar and Ar^1 are both aromatic groups they may be like or unlike. Ar and Ar^1 may both be monocyclic aromatic groups and Ar^1 may be a heteromonocyclic group which may contain a nuclear nitrogen atom with or without an additional nuclear hetero atom.]

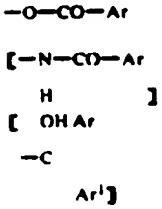
The [compounds] *compound* of the present invention [are] *is* useful as [medicaments] *a medicament* especially in the treatment of cardiovascular conditions.

In earlier patent applications we have described compounds having the general formula:

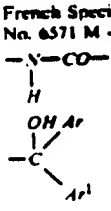


(II)

in which A *is substantially a tertiary aliphatic, cycloaliphatic or heterocyclo amino group* and R [have substantially the same meanings as in formula I above,] *is substantially a straight or branched chain lower alkyl group*, and X respectively represents the following groupings in the various cases:



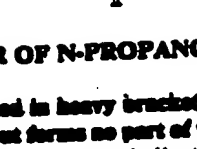
French Special Medicine Pat. No. 6571 M - 352 CAM



French Special Medicine Pat. No. 7700 M

French Pat. No. 70/00018

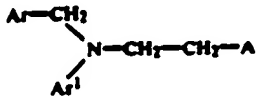
-continued



French Pat. No. 69/24445

wherein Ar is an aromatic group and Ar^1 is an aromatic or heterocyclic group.

Moreover, compounds having the following general formula are already known for their properties as anti-histamines:

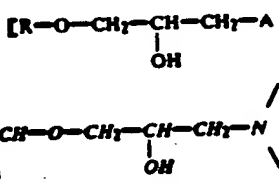


(III)

in which A has the same meaning as [in the general formulae I and II] *indicated* above, whilst Ar and Ar^1 are aromatic groups. (Ehrhart/Ruschig Arzneimittel I, pages 208–210).

The [compounds] *compound* according to the present invention having the [general] formula I, [are] *is* manifestly different from any of these groups of compounds.

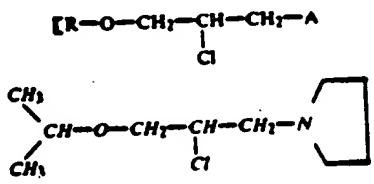
The [compounds] *compound* of the present invention may be prepared from *an* amino [alcohols] *alcohol* having the [general] formula:



(IV)

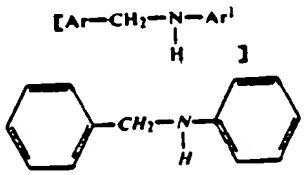
[in which A and R are as defined above in connection with formula I.]

In the first step of such preparation, the amino [alcohols] *alcohol* (IV), which [are] *is a* known [materials] *material*, and [are] *is* described inter alia in Belgium Pat. No. 718 425, [are] *is* treated with thionyl chloride dissolved in a suitable solvent such as chloroform in order to obtain the corresponding chloro [compounds] *compound* having the [general] formula:



(V)

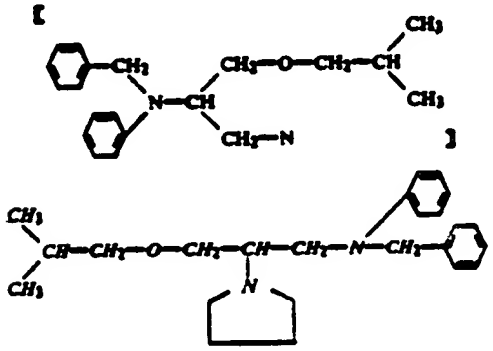
The latter [compounds are] *compound is* then condensed with [amines] *an amine* having the [general] formula



which [have] *has* previously been converted to [their] *its* sodium [derivatives] *derivative* by reaction with sodium amide, to obtain the [compounds] *compound* of the present invention.

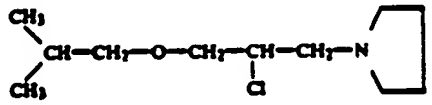
The invention also includes the addition salts of the [compounds] *compound* having the [general] formula I with pharmaceutically acceptable organic and inorganic acids such as hydrochloric acid and fumaric acid.

[As an] *An* example of the process of the invention [there] will now be described *for* the synthesis of [1-(3-isobutoxy-2-(phenylbenzyl)-amino)-propyl-pyrrolidine-hydrochloride (Compound No. 1).] *1-isobutoxy-2-pyrrolidino-3-N-benzylanilino propane hydrochloride (Compound 1).*



First step

Preparation of 1-(3-isobutoxy-2-chloro)propyl pyrrolidine



345 ml of thionyl chloride dissolved in 345 ml of chloroform are added, drop by drop, to 275 g of 1(3-isobutoxy-2-hydroxy)-propyl-pyrrolidine dissolved in 350 ml of chloroform, while maintaining the temperature at approximately 45° C. The reaction mixture is heated to reflux until gas is no longer evolved. The chloroform and the excess of thionyl chloride are removed under reduced pressure. The residue is poured on to 400 g of crushed ice. The reaction mixture is rendered alkaline with soda and the resulting mixture is extracted twice with 250 ml of diethyl ether. The combined ethereal extracts are dried over anhydrous sodium sulphate. After evaporation of the solvent the residue is distilled under reduced pressure: 220 g of product are obtained having the following properties:

Boiling point = 96° C./3 mm, $n_D^{24°\,C.} = 1,4575$.

Second step

Main product

23.4 g of sodium amide is added little by little to a solution of 92 g of N-benzylaniline in 500 ml of anhydrous xylene. The reaction mixture is then heated at 130° to 135° C. for 6 hours.

Whilst maintaining the temperature at 110° C., 110 g of the product of the first step dissolved in 150 ml of xylene is added and the product heated for 6 hours at 120° C.

The product having been allowed to cool to ambient temperature, 200 ml of cold water are added. The organic phase is separated and extracted with an aqueous solution of hydrochloric acid.

After twice washing with 100 ml of diethyl ether, the aqueous phase is made alkaline with 50% caustic soda solution. The liberated base is twice extracted with 150 ml of diethyl ether. After the ether has been evaporated, the residue is distilled under reduced pressure and has Bpt = 184° C./0.1 mm, $n_D^{20} = 1.5538$.

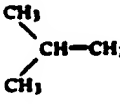
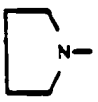
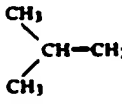
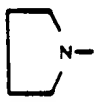
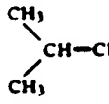
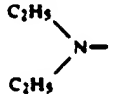
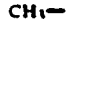
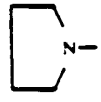
77 g of the pure base in the form of a viscous liquid is thus obtained.

The hydrochloride, which is prepared in conventional manner, has a melting point of 128° C.

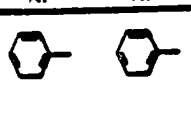
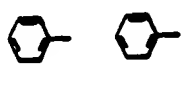
Analysis	C%	H%	N%
Calculated:	71.52	8.75	6.95
Found:	71.20	9.01	6.93

[Table I which follows sets out a series of products according to the present invention which were obtained using the foregoing method but substituting the appropriate intermediates containing the desired groups R and A and Ar and Ar^1 respectively.]

[TABLE I

COMPOUND No.	Ar	Ar^1	R	A	Melting Points of Salts °C.	ANALYSIS C% Theory	C% Found	H% Theory	H% Found	N% Theory	N% Found
1					Hydrochloride 128°	71.52	71.20	8.75	9.01	6.95	6.93
2					Fumarate 150°	67.08	66.90	7.66	7.20	8.69	8.75
3					Fumarate 98°	69.39	69.46	8.31	8.34	5.77	5.72
4					Fumarate 155°	68.16	68.42	7.32	7.30	6.35	6.31

[TABLE I-continued

COM-POUND No.	Ar	Ar¹	R	A	Melting Point of Salts °C.	ANALYSIS C% Theory	C% Found	H% Theory	H% Found	N% Theory	N% Found
5					Fumarate 195°	67.44	67.90	7.68	7.78	5.61	5.64
6					Hydrochloride 133°	74.55	74.09	7.82	7.40	6.21	6.14

]

The pharmacological activity of the [compounds] *compound* of the invention in the cardiovascular field was determined on the dog in the manner described below:

An incision is made in the right-hand chest wall of an animal, which has been anaesthetised with chloralose and given artificial respiration, to enable the blood from the venus sinus to be drawn off and the apparatus required to record the following parameters to be inserted in position:

a. Output of the coronary sinus;
b. P_aO_2 of the blood from the coronary sinus; and
c. Amplitude of the contractions of the right ventricule.

At the same *time* there were also measured:

d. Arterial pressure in a main carotid artery; and
e. The rate of heart-beat determined cardiotachometrically.

Table II which follows records the determinations made of the various parameters, the results being expressed as a maximum percentage variation relative to the pre-treatment values.

It then seemed interesting [, using compound No. 1,] to seek the existence of an action on the β-adrenergic receptors in the manner outlined below:

A stimulating electrode was placed in position on the right stellar ganglion of dogs anaesthetised as described above and for which there were recorded:

a. The arterial pressure,
b. Ventricular inotropism (the amplitude of contraction of the right ventricle), and
c. The rate of heart-beat.

The chest of the animals were not open and they were breathing freely.

The β-adrenergic receptors, both cardiac and vascular, were stimulated by electrical stimulation of the right stellar ganglion or by intravenous injection with isoprenaline (5 μg/kg). The measurements were taken both before and after administration of compound No. 1 by the intravenous route in a dose of 5 mg/kg bodyweight.

The following Table III gives the average percentage inhibition of the cardiovascular effects of isoprenaline and of the cardiac effects of the stimulation of the right

TABLE II

COM-POUND No.	DOSE mg/kg (intravenous)	NUMBER OF ANIMALS	CORONARY OUTPUT %	RATE OF HEART-BEAT %	P_aO_2 %	ARTERIAL PRESSURE %	AMPLITUDE OF VENTRICULAR CONTRACTION %
1	2.5	7	+51.2	−28.6	+119.2	−39.8	−0.7
	5	7	+36.9	−31.8	+120.8	−40.2	−22.3
[2	5	3	+55	−28	+71	−43	−25.5]
[3	5	4	+117.8	−19.2	+158	−30.5	−3]
[4	5	4	+110.5	−14.9	−56	−26	+17.5]
[5	5	3	+24	−3.5	+11.6	−15	+1.5]

These results show that, taken as a whole, the [products] *product* under examination [have] *has* the ability to increase the output of cornary blood, to reduce the rate of heart beat and especially [, with the exception of compound No. 4,] to increase the oxygen content of the venous cardiac blood. The latter action is demonstrated by an excess in the supply of oxygen relative to the requirements of the myocardium. The arterial pressure is also lowered for a short time. [In most cases there] *There* is little alteration in the ventricular inotropism.

Particular note should be taken [, in the case of compound No. 1,] of the very considerable increase in the oxygen content of the venous cardiac blood in relation to the increase in coronary output, which may be simply attributed to the improved circulation of the blood. The extremely slow rate of heart-beat brought about by the products certainly plays an important role in this respect.

stellar ganglion.

TABLE III

	Number of Animals	Hypotension	Rate of Heart-beat	Positive inotropic effect
ISOPRENALINE [(5 γ/kg) *(5 μg/kg* intravenous)	4	−54%	−32.7%	−46.5%
STIMULATION OF THE RIGHT STELLAR GANGLION	3		−30%	−21.3%

These results show that a partial inhibiting effect is achieved as regards the β-adrenergic receptors at the cardiovascular level of treatment.

In conclusion, it is apparent that the [members of the series of compounds possess] *compound possesses* a distinct cardio-vascular activity which is manifested by an improvement in circulation by the enhanced oxyge-

nation of the myocardium in consequence of a slow rate of heart-beat.

In addition to the general properties [of the compounds of the present invention,] compound No. 1 is also of interest in that it also possesses inhibiting effects with respect to the stimulation of the β-adrenergic receptors.

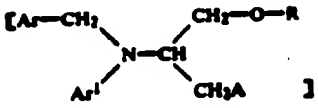
The pharmacological activities of [the compounds having the general formula] *compound* I thus [enable their] *enables its* application in human therapy to be anticipated, as [medicaments] *a medicament* intended for treating particularly:

Myocardian anoxaemia,
Coronary deficiencies, angina pectoris,
Infarction of the myocardium, and
Cardiac deficiencies associated with coronary circulatory trouble.

When admixed with the usual excipients, [they] *it* may be administered orally or rectally, in daily doses of between 100 and 800 mg.

What we claim is:

[1. An ether of n-propanolamine having the formula]



[wherein A is morpholino, pyrrolidino, piperidyl, and di-lower-alkyl amino, R is a straight or branched chain lower alkyl, or benzyl, Ar is aryl and Ar^1 is aryl or pyridyl, and pharmacologically acceptable salts thereof.]

[2. The ether of claim 1 in which A is pyrrolidino, R is isobutyl and Ar and Ar^1 are both phenyl, and the hydrochloride thereof.]

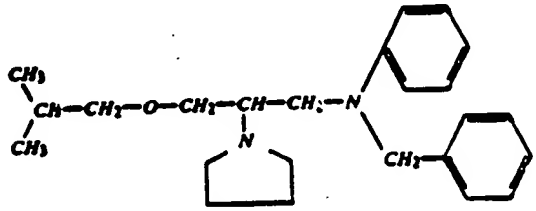
[3. The ether of claim 1 in which A is pyrrolidino, R is isobutyl, Ar is phenyl and Ar^1 is 2-pyridyl, and the acid fumarate thereof.]

[4. The ether of claim 1 in which A is diethylamino, R is an isobutyl and Ar and Ar^1 are both phenyl, and the acid fumarate thereof.]

[5. The ether of claim 1 in which A is morpholino, R is isobutyl and Ar and Ar^1 are both phenyl and the acid fumarate thereof.]

[6. The ether of claim 1 in which A is piperidyl, R is benzyl and Ar and Ar^1 are both phenyl and the hydrochloride thereof.]

7. An ether having the formula



and pharmaceutically acceptable acid addition salts thereof.

8. An ether according to claim 7 wherein the acid addition salt is the hydrochloride or the acid fumarate.

* * * * *

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"ATTACHMENT B"

United States Patent [19]

Mauvernay et al.

[11] **3,962,238**

[45] **June 8, 1976**

[54] **ETHERS OF N-PROPANOL AMINE**

[75] Inventors: **Roland Yves Mauvernay**, Riom; **Norbert Busch**, Loubeyrat; **Jacques Moleyre**, Mozac; **André Monteil**, Gerzat; **Jacques Simond**, Chamalieres, all of France

[73] Assignee: **Centre Europeen de Recherches Mauvernay "CERM"**, Riom, France

[22] Filed: **Feb. 27, 1973**

[21] Appl. No.: **336,357**

[30] **Foreign Application Priority Data**

Mar. 6, 1972 France 72.07647

[52] **U.S. Cl.** ..... **260/247.2 B**; 260/247.5 R; 260/293.79; 260/296 AE; 260/326.5 L; 260/326.5 R; 260/570.6; 260/570.9; 260/573; 424/248; 424/267; 424/274; 424/325

[51] **Int. Cl.²** **C07D 295/00**

[58] **Field of Search** ..... 260/326.5 L, 247.2 B, 260/247.5 R, 293.76, 296 AE, 570.9, 570.6, 573

[56] **References Cited**

UNITED STATES PATENTS

2,600,301	6/1952	Kerwin	260/570.9
2,832,795	4/1958	Hempel et al.	260/570.9
3,666,811	5/1972	Van der Stcldt	260/570.9

Primary Examiner—Paul J. Killos
Attorney, Agent, or Firm—Haseltine, Lake & Waters

[57] **ABSTRACT**

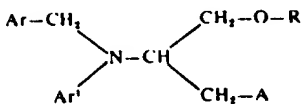
Ethers of n-propanolamine, preparation thereof and their use in treatment of cardiovascular conditions.

6 Claims, No Drawings

ETHERS OF N-PROPANOL AMINE

This invention relates to ethers of n-propanolamine, to the preparation thereof and to the use thereof.

The present invention provides an ether of an n-propanolamine having the general formula:



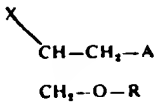
(I)

in which A is a tertiary aliphatic, cycloaliphatic or heterocyclic amino group, R is a straight or branched chain lower alkyl group or an aralkyl group, Ar is an aromatic group and Ar' is an aromatic or heterocyclic group, and addition salts thereof with pharmacologically acceptable acids.

When Ar and Ar' are both aromatic groups they may be like or unlike. Ar and Ar' may both be monocyclic aromatic groups and Ar' may be a heteromonocyclic group which may contain a nuclear nitrogen atom with or without an additional nuclear hetero atom.

The compounds of the present invention are useful as medicaments especially in the treatment of cardiovascular conditions.

In earlier patent applications we have described compounds having the general formula:

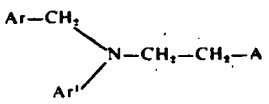


(II)

in which A and R have substantially the same meanings as in formula I above, and X respectively represents the following groupings in the various cases:

—O—CO—Ar	French Special Medicine Patent No. 6571 M - 352 CAM
—N—CO—Ar H	French Special Medicine Patent No. 7700 M
OH —C Ar'	French Patent No. 70/00018
H —C Ar'	French Patent No. 69/24645

Moreover, compounds having the following general formula are already known for their properties as antihistamines:

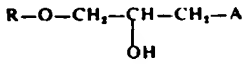


(III)

in which A has the same meaning as in the general formulae I and II above, whilst Ar and Ar' are aromatic groups. (Ehrhart/Ruschig Arzneimittel I, pages 208–210).

The compounds according to the present invention having the general formula I, are manifestly different from any of these groups of compounds.

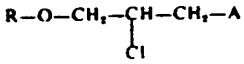
The compounds of the present invention may be prepared from amino alcohols having the general formula:



(IV)

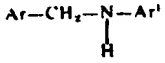
in which A and R are as defined above in connection with formula I.

In the first step of such preparation, the amino alcohols (IV), which are known materials, and are described inter alia in Belgium Pat. No. 718 425, are treated with thionyl chloride dissolved in a suitable solvent such as chloroform in order to obtain the corresponding chloro compounds having the general formula:



(V)

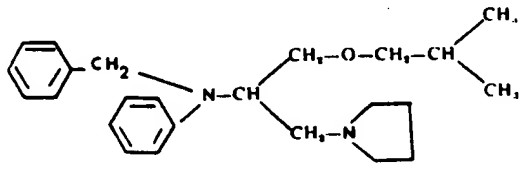
The latter compounds are then condensed with amines having the general formula



which have previously been converted to their sodium derivatives by reaction with sodium amide, to obtain the compounds of the present invention.

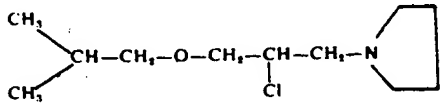
The invention also includes the addition salts of the compounds having the general formula I with pharmaceutically acceptable organic and inorganic acids such as hydrochloric acid and fumaric acid.

As an example of the process of the invention there will now be described the synthesis of 1-(3-isobutoxy-2-(phenylbenzyl)-amino)-propyl-pyrrolidino-hydrochloride (Compound No. 1).



First step

Preparation of 1-(3-isobutoxy-2-chloro)propyl pyrrolidine



345 ml of thionyl chloride dissolved in 345 ml of chloroform are added, drop by drop, to 275 g of 1(3-isobutoxy-2-hydroxy)-propyl-pyrrolidine dissolved in 350 ml of chloroform, while maintaining the temperature at approximately 45°C. The reaction mixture is heated to reflux until gas is no longer evolved. The chloroform and the excess of thionyl chloride are removed under reduced pressure. The residue is poured on to 400 g of crushed ice. The reaction mixture is rendered alkaline with soda and the resulting mixture is extracted twice with 250 ml of diethyl ether. The combined ethereal extracts are dried over anhydrous sodium sulphate. After evaporation of the solvent the residue is distilled under reduced pressure: 220 g of product are obtained having the following properties:

Boiling point = 96°C/3 mm, $n_D^{24°C}$ = 1.4575,

Second step

Main product

ml of diethyl ether. After the ether has been evaporated, the residue is distilled under reduced pressure and has Bpt = 184°C/0.1 mm, n_D^{20} = 1.5538.

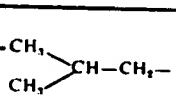
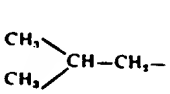
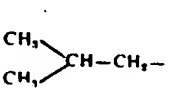
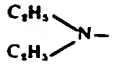
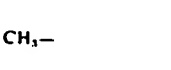
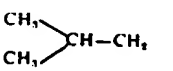
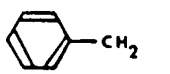
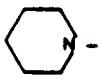
77 g of the pure base in the form of a viscous liquid is thus obtained.

The hydrochloride, which is prepared in conventional manner, has a melting point of 128°C.

Analysis	C%	H%	N%
Calculated:	71.52	8.75	6.95
Found:	71.20	9.01	6.93

Table I which follows sets out a series of products according to the present invention which were obtained using the foregoing method but substituting the appropriate intermediates containing the desired groups R and A and Ar and Ar' respectively.

TABLE I

COMPOUND No.	Ar	Ar'	R	A	Melting Points of Salts °C	ANALYSIS C% Theory	C% Found	H% Theory	H% Found	N% Theory	N% Found
1					Hydrochloride 128°	71.52	71.20	8.75	9.01	6.95	6.93
2					Fumarate 150°	67.08	66.90	7.66	7.20	8.69	8.75
3					Fumarate 98°	69.39	69.46	8.31	8.34	5.77	5.72
4					Fumarate 155°	68.16	68.42	7.32	7.30	6.35	6.31
5					Fumarate 195°	67.44	67.90	7.68	7.76	5.61	5.64
6					Hydrochloride 133°	74.55	74.05	7.82	7.40	6.21	6.14

23.4 g of sodium amide is added little by little to a solution of 92 g of N-benzylaniline in 500 ml of anhydrous xylene. The reaction mixture is then heated at 130° to 135°C for 6 hours.

Whilst maintaining the temperature at 110°C, 110 g of the product of the first step dissolved in 150 ml of xylene is added and the product heated for 6 hours at 120°C.

The product having been allowed to cool to ambient temperature, 200 ml of cold water are added. The organic phase is separated and extracted with an aqueous solution of hydrochloric acid.

After twice washing with 100 ml of diethyl ether, the aqueous phase is made alkaline with 50% caustic soda solution. The liberated base is twice extracted with 150

The pharmacological activity of the compounds of the invention in the cardiovascular field was determined on the dog in the manner described below:

An incision is made in the right-hand chest wall of an animal, which has been anaesthetised with chloralose and given artificial respiration, to enable the blood from the venus sinus to be drawn off and the apparatus required to record the following parameters to be inserted in position:

a. Output of the coronary sinus;

b. P_tO_2 of the blood from the coronary sinus; and

c. Amplitude of the contractions of the right ventricule.

At the same there were also measured:

d. Arterial pressure in a main carotid artery: and

e. The rate of heart-beat determined cardiotachometrically.

Table II which follows records the determinations made of the various parameters, the results being expressed as a maximum percentage variation relative to the pre-treatment values.

TABLE II

COMPOUND No.	DOSE mg/kg. (intravenous)	NUMBER OF ANIMALS	CORONARY OUTPUT %	RATE OF HEART-BEAT %	SINUSAL P_aO_2 %	ARTERIAL PRESSURE %	AMPLITUDE OF VENTRICULAR CONTRACTION %
1	2.5	7	+51.2	−28.6	+119.2	−39.8	−0.7
	5	7	+36.9	−31.8	+120.8	−40.2	−22.3
2	5	3	+55	−28	+71	−43	−25.5
3	5	4	+117.8	−19.2	+158	−30.5	−3
4	5	4	+110.5	−14.5	−56	−26	+17.5
5	5	3	+24	−3.5	+11.6	−15	+1.5

These results show that, taken as a whole, the products under examination have the ability to increase the output of coronary blood, to reduce the rate of heart beat and especially, with the exception of compound No. 4, to increase the oxygen content of the venous cardiac blood. The latter action is demonstrated by an excess in the supply of oxygen relative to the requirements of the myocardium. The arterial pressure is also lowered for a short time. In most cases there is little alteration in the ventricular inotropism.

Particular note should be taken, in the case of compound No. 1, of the very considerable increase in the oxygen content of the venous cardiac blood in relation to the increase in coronary output, which may be simply attributed to the improved circulation of the blood. The extremely slow rate of heart-beat brought about by the products certainly plays an important role in this respect.

It then seemed interesting, using compound No. 1, to seek the existence of an action on the β-adrenergic receptors in the manner outlined below:

A stimulating electrode was placed in position on the right stellar ganglion of dogs anaesthetised as described above and for which there were recorded:

a. The arterial pressure,

b. Ventricular inotropism (the amplitude of contraction of the right ventricle), and

c. The rate of heart-beat.

The chest of the animals were not open and they were breathing freely.

The β-adrenergic receptors, both cardiac and vascular, were stimulated by electrical stimulation of the right stellar ganglion or by intravenous injection with isoprenaline (5 μg/kg). The measurements were taken both before and after administration of compound No. 1 by the intravenous route in a dose of 5 mg/kg bodyweight.

The following Table III gives the average percentage inhibition of the cardiovascular effects of isoprenaline and of the cardiac effects of the stimulation of the right stellar ganglion.

TABLE III

	Number of animals	PERCENTAGE INHIBITION OF Hypotension	Rate of Heart-beat	Positive inotropic effect
ISOPRENALINE (5 ug/kg Intravenous)	4	−54%	−32.7%	−46.5%
STIMULATION OF THE RIGHT STELLAR GANGLION	3		−30%	−21.3%

These results show that a partial inhibiting effect is achieved as regards the β-adrenergic receptors at the cardiovascular level of treatment.

In conclusion, it is apparent that the members of the series of compounds possess a distinct cardio-vascular activity which is manifested by an improvement in circulation by the enhanced oxygenation of the myocardium in consequence of a slow rate of heart-beat.

In addition to the general properties of the compounds of the present invention, compound No. 1 is also of interest in that it also possesses inhibiting effects with respect to the stimulation of the β-adrenergic receptors.

The pharmacological activities of the compounds having the general formula I thus enable their application in human therapy to be anticipated, as medicaments intended for treating particularly:

Myocardiac anoxaemia,

Coronary deficiencies, angina pectoris,

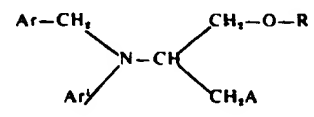
Infarction of the myocardium, and

Cardiac deficiencies associated with coronary circulatary trouble.

When admixed with the usual excipients, they may be administered orally or rectally, in daily doses of between 100 and 800 mg.

What we claim is:

1. An ether of n-propanolamine having the formula



wherein A is morpholino, pyrrolidino, piperidyl, and di-lower-alkyl amino, R is a straight or branched chain lower alkyl, or benzyl, Ar is aryl and Ar^1 is aryl or pyridyl, and pharmacologically acceptable salts thereof.

2. The ether of claim 1 in which A is pyrrolidino, R is isobutyl and Ar and Ar' are both phenyl, and the hydrochloride thereof.

3. The ether of claim 1 in which A is pyrrolidino, R is isobutyl, Ar is phenyl and Ar' is 2-pyridyl, and the acid fumarate thereof.

4. The ether of claim 1 in which A is diethylamino, R is an isobutyl and Ar and Ar' are both phenyl, and the acid fumarate thereof.

5. The ether of claim 1 in which A is morpholino, R is isobutyl and Ar and Ar' are both phenyl and the acid fumarate thereof.

6. The ether of claim 1 in which A is piperidyl, R is benzyl and Ar and Ar' are both phenyl and the hydrochloride thereof.

* * * * *

"ATTACHMENT C"

Following is a brief description of the activities undertaken by Wallace Laboratories and McNeilab, Inc. during the applicable regulatory review period with respect to bepridil hydrochloride and the significant dates applicable to such activities:

February 18, 1977	IND covering bepridil hydrochloride mailed to FDA by Wallace Laboratories.
February 22, 1977	IND received and accorded IND No. 13,238.
March 7, 1977	Clinical hold imposed on IND No. 13,238.
September 7, 1977	Wallace Laboratories letter confirms agreement to submit all Phase I and early Phase II protocols to FDA prior to study initiations.
September 7, 1977	Protocol (77017-01) for Phase I dose-tolerance study submitted by Wallace Laboratories.
September 7, 1977	Final report initial Phase I single dose study submitted by Wallace Laboratories.
October 7, 1977	Documentation of IND Clinical Trials protocols submitted by Wallace Laboratories.
February 24, 1978	Annual progress report submitted by Wallace Laboratories.
April 11, 1978	Clinical hold recinded by FDA.
April 11, 1978	Protocol (78011-01) calling for parallel comparison of graduated doses of bepridil hydrochloride submitted by Wallace Laboratories.
April 11, 1978	Protocol (77017-01) Final Report submitted by Wallace Laboratories.
January 30, 1979	Annual progress report submitted by Wallace Laboratories.
May 9, 1979	Protocol (78011-01) final report submitted by Wallace Laboratories.

May 9, 1979	Protocol (79003) study of antianginal activity of bepridil hydrochloride submitted by Wallace Laboratories.
August 3, 1979	Requested amendments to Protocol (79003) submitted by Wallace Laboratories.
October 12, 1979	Protocol (79024) comparing the efficacy and tolerability of bepridil hydrochloride to propranolol hydrochloride submitted by Wallace Laboratories.
January 31, 1980	Annual progress report submitted by Wallace Laboratories.
May 28, 1980	Protocol (79052) identical to Protocol (79024) covering additional clinical trials submitted by Wallace Laboratories.
June 13, 1980	Protocol (79053) identical to Protocol (79003) covering additional clinical trials submitted by Wallace Laboratories.
July 30, 1980	Protocol to study pharmakinetics and tolerability of bepridil hydrochloride at doses of 300; 400; 500 and 600 mg. submitted by Wallace Laboratories.
December 15, 1980	Protocol (13238-PO1A) to study the cardiac function of 500 mg. doses of bepridil hydrochloride submitted by Wallace Laboratories.
December 15, 1980	Protocol (13,238-PO2) to study pharmakinetics and tolerability of 400 mg. doses of bepridil hydrochloride submitted by Wallace Laboratories.
December 29, 1980	Protocol to study pharmakinetics and tolerability of 200; 300 and 400 mg. doses of bepridil hydrochloride submitted by Wallace Laboratories.
January 30, 1981	Annual progress report submitted by Wallace Laboratories.
February 13, 1981	Protocol (13238-HO5) covering multicenter clinicals to demonstrate hypertensive activity of bepridil hydrochloride submitted by Wallace Laboratories.
February 13, 1981	Protocol (13238-HO6) having same objective as Protocol (13238-HO5) submitted by Wallace Laboratories.

February 18, 1981	Amendment to Protocol (13238-P02) submitted by Wallace Laboratories.
February 20, 1981	Amendment to Protocol (13238-P01A) submitted by Wallace Laboratories.
February 20, 1981	Protocol (13238-A03) treatment of angina pectoris with bepridil hydrochloride submitted by Wallace Laboratories.
April 27, 1981	Protocol (13238-1405) treatment of mild to moderate hypertension with bepridil hydrochloride submitted by Wallace Laboratories.
April 28, 1981	Protocol (13238-06) amended by Wallace Laboratories.
January 29, 1982	Annual progress report filed by Wallace Laboratories.
February 15, 1982	McNeil Pharmaceutical files IND covering bepridil hydrochloride.
February 15, 1982	McNeil's application received by FDA and accorded IND No. 19,896 effective March 17, 1982.
June 7, 1982	End of Phase II report issued by FDA.
January 28, 1983	Annual progress report submitted by Wallace Laboratories.
April 12, 1983	Pre-NDA submission by Wallace Laboratories and McNeil - Manufacturing controls/preclinical data.
April 12, 1983	McNeil letter authorizes FDA to refer to McNeil manufacturing controls/preclinical data in connection with Wallace Laboratories IND 13,238.
July 22, 1983	Clinical study (CS83047) covering the bioavailability of bepridil hydrochloride submitted by Wallace Laboratories.
September 29, 1983	Clinical study (CS83109) covering the bioavailability of bepridil hydrochloride submitted by Wallace Laboratories.
November 9, 1983	Clinical studies relating to the effectiveness and safety of bepridil hydrochloride submitted by Wallace Laboratories.

December 28, 1983	Wallace Laboratories and McNeil simultaneously and cooperatively file NDAs for bepridil hydrochloride (Wallace Laboratories BEPADIN NDA 1900-1 and McNeil VASCOR NDA 1900-2).
December 28, 1983	Clinical studies treatment of angina in general patient population submitted by McNeil.
February 14, 1984	Annual progress report update on information included in NDA filings filed by Wallace Laboratories and McNeil.
May 8, 1984	Drug Safety update covering the period December 1, 1983 - February 29, 1984 submitted by Wallace Laboratories and McNeil.
September 28, 1984	Phase III Protocol (#133) comparison of bepridil hydrochloride with diltiazem to be conducted under clinical study (CS84033) submitted.
October 22, 1984	Patent information submitted.
January 31, 1985	Safety information updates submitted to FDA.
February 1, 1985	Annual progress reports submitted to FDA.
February 21, 1985	Protocol (#138) to study bepridil hydrochloride in the long term therapy of stable, chronic angina in usual clinical practice submitted.
March 12, 1985	Identity of 24 physicians participating in clinical studies under Protocol (#138) submitted to FDA.
June 19, 1985	Protocol (#139) comparing safety and efficacy of bepridil hydrochloride against propranolol submitted.
June 27, 1985	Safety update submitted by McNeil.
July 1, 1985	Safety update submitted by Wallace Laboratories.
July 19, 1985	Protocol (#140) comparing safety and efficacy of bepridil hydrochloride against inifedipine submitted.

August 2, 1985	Meeting amongst FDA/Wallace Laboratories/McNeil adverse clinical reactions.
August 6, 1985	Letter to FDA from Wallace Laboratories advising of suspension of clinical trials of bepridil hydrochloride in light of adverse experiences.
November 21, 1985	Meeting amongst FDA/Wallace Laboratories/McNeil - status of NDA 1900-1 and NDA 1900-2.
December 13, 1985	Letter to FDA acknowledging intention to proceed with NDAs and agreement to attend Cardio-Renal Advisory Committee meeting.
February 1, 1986	Annual Progress Report filed.
February 10, 1986	Patent information update filed.
March 27, 1986	Cardio-Renal Advisory Committee meeting attended by Wallace Laboratories and McNeil.
June 6, 1986	Not approvable letter mailed to Wallace Laboratories and McNeil by FDA.
June 26, 1986	Letter from Wallace Laboratories to FDA advising of intent to amend NDA based on data obtained from McNeil investigations.
July 2, 1986	Meetings amongst FDA/Wallace Laboratories/McNeil directed to the establishment of protocols under which the safety and efficacy of bepridil hydrochloride will be evaluated.
July 10, 1986	Meetings amongst FDA/Wallace Laboratories/McNeil directed to the establishment of protocols under which the safety and efficacy of bepridil hydrochloride will be evaluated.
July 16, 1986	Meetings amongst FDA/Wallace Laboratories/McNeil directed to the establishment of protocols under which the safety and efficacy of bepridil hydrochloride will be evaluated.
August 15, 1986	Meetings amongst FDA/Wallace Laboratories/McNeil directed to the establishment of protocols under which the safety and efficacy of bepridil hydrochloride will be evaluated.

February 18, 1987	Annual progress report filed.
September 28, 1987	Safety update report filed.
December 28, 1988	Clinical trial results (Protocol BR) directed to the safety and efficacy of bepridil hydrochloride in the treatment of patients who are refractory or intolerant of other antianginal prophylaxis reported by McNeil.
December 28, 1988	McNeil amends NDA 1900-02.
January 9, 1989	Wallace Laboratories amends NDA 1900-01 by reference to McNeil NDA.
January 27, 1989	FDA acknowledges receipt of Wallace Laboratories January 9, 1989, amendment and advises that amendment is major and will require an additional 180 day period for review.
May 4, 1989	Annual progress report filed by McNeil.
May 22, 1989	Wallace Laboratories references McNeil's May 4, 1989 submission.
June 13, 1989	NDA 1900-02 amended by McNeil.
June 13, 1989	Draft SBA submitted by McNeil.
July 5, 1989	Wallace Laboratories references McNeil's June 13, 1989 submissions.
April 2, 1990	Safety update submitted by McNeil.
April 23, 1990	Annual report submitted by McNeil.
May 1, 1990	Wallace Laboratories references McNeil's April 2, 1990 submission.
June 5, 1990	Wallace Laboratories references McNeil's April 23, 1990 Annual Report.
December 28, 1990	Approval letter for marketing BEPADIN/VASCOR mailed by FDA to Wallace Laboratories and McNeil.